UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/631,152	08/02/2000	Jon A. Wolff	Mirus.017.01	8109

7590 08/26/2003

Mark K. Johnson
P. O. Box 510644
New Berlin, WI 53131-0644

EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/631,152	WOLFF ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-33* is/are pending in the application.

4a) Of the above claim(s) *18-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is a response to the "Amendment under 37 CFR §1.111" filed 16 June 2003 (Paper No. 14) in reply to the Non-Final Office action mailed 16 December 2002 (Paper No. 13). Claims 18-33 were withdrawn from consideration and claims 1-17 were considered in Paper No. 13. Claim 2 was canceled and claims 1 and 3 were amended in Paper No. 14. Claims 1 and 3-33 are pending and claims 1 and 3-17 are under consideration herein.

Election/Restrictions

This application contains claims 18-33 drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Amendment

Rejection of claim 2 is rendered moot by cancellation thereof.

Claim Rejections - 35 USC § 112

Claims 1 and 3-17 stand rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for reasons of record and herein below in the response to arguments.

Claims 1and 3-17 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons of record and herein below in the response to arguments.

Claims 5, 6, and 14-17 stand rejected under 35 U.S.C. 112, second paragraph, as indefinite. Applicant does not address these grounds for rejection in the reply; therefore, the claims stand rejected for reasons of record.

Claim Rejections - 35 USC § 102

Rejection of claims 1, 3-9 and 13 under 35 U.S.C. 102(b) as anticipated by Leahy *et al.* (1996; IDS Paper No. 4, Item #5) as evidenced by Pierce Chemical Technical Library publication "Other Biotinylation Reagents: Immunopure® Photoactivatable Biotin" available at http://www.piercenet.com is withdrawn in view of the amendments.

Rejection of claims 1, 7 and 13 under 35 U.S.C. 102(b) as anticipated by Ireland *et al.* (1987) *FEBS Lett.* 212:173-176 is withdrawn in view of the amendments.

Response to Arguments

The attachment identified in the amendment as a Declaration under 37 CFR §1.132 is not a proper Declaration. As there is no signature accompanying the preprint it is not clear who is making the Declaration. Therefore, the preprint submitted with the Amendment will be considered an exhibit, and the published article (i.e., Slattum *et al.*(2003) *Mol. Ther.* 8:255-263) is hereby made of record.

Claim Rejections - 35 USC § 112

Claims 1 and 3-17 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant does not respond directly to the written description rejection. However, some of the arguments set forth in the response to the enablement rejection appear to be an attempt to rebut the *prima facie* finding of inadequate written description. Those arguments will therefore be addressed first in view of the written description requirement and then in view of the enablement requirement of 35 U.S.C. §112, first paragraph.

In response to the rejections of record, Applicant has amended the claims such that they are now limited to attaching a "nucleic acid modifying agent" to the nucleic acid molecule. Although the amendment renders the claims indefinite for the reasons set forth herein below under "New Grounds Necessitated by Amendment", the claims are understood to encompass attaching any compound to a DNA molecule, according to their broadest reasonable interpretation. In the fourth paragraph on page 9, Applicant argues that, because the compounds reduced to practice fall into various categories, the full scope of those categories, and the full scope of the modifying agent of the claims is adequately described. This argument has been fully considered but is not found persuasive because the relevant identifying characteristic of the genus is not whether it is a hapten, an antigen, a ligand or a fluorescent molecule, but whether it can be incorporated into an expressible sequence without disrupting expression. As pointed out in the previous Office Action, the attributes common to the genus of compounds capable of

being attached within an expressible sequence without disrupting expression are unknown in the art and therefore unpredictable. Because Applicant has not described the nucleic acid modifying agent such that the skilled artisan could distinguish nucleic acid modifying agents that could be used in the claimed method from nucleic acid modifying agents that could not be used in the claimed method, the skilled artisan would not have recognized that Applicant was in possession of the full scope of the claimed subject matter at the time of filing. Therefore, for these reasons and reasons of record in the previous Office Action, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

Claims 1and 3-17 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for nucleic acid delivery to a cell *in vitro*, comprising: (a) preparing a nucleic acid molecule having an expressible sequence; (b) attaching a compound to the nucleic acid molecule tithing the expressible sequence, utilizing a modifying chemical attachment; and, (c) delivering the nucleic acid to a cell where the expressible sequence is expressed, wherein said compound is selected from the group consisting of rhodamine, DNP, digoxin, biotin, and the peptide nuclear localization sequence CPKKKRKVEDG, does not reasonably provide enablement for a process for nucleic acid delivery to a cell *in vivo* or a process for nucleic acid delivery to a cell *in vitro* wherein the compound is *any* and *all* compounds or nuclear localizing signals, ligands that binds a receptor, releasing signals, enhanced immune response molecules, antigens, antibodies, haptens, membrane active compounds, peptides, polymers, polyions and fluorescent compounds.

As described above, Applicant argues that the claims are enabled for the full scope of nucleic acid modifying agents because the examples provided are representative of a wide variety of compounds. This argument has been fully considered but is not found persuasive because it fails to account for the tremendous scope of the claims which are directed to using any and all nucleic acid modifying agents, and the lack of guidance with regard to which nucleic acid modifying agents could be used in the claimed method. Although the presence of inoperative embodiments within the scope of the claim does not necessarily render a claim non-enabled, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. "The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414; hereinafter *Atlas*). Given the tremendous number of compounds encompassed by nucleic acid modifying agents, the unpredictability of obtaining expression of an expressible sequence after attachment of any given modifying agent and the absence of teachings in the specification that would enable the skilled artisan to identify modifying agents that could be used in the method without resorting to blind trial and error experimentation, the skilled artisan clearly cannot determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.

Regarding enablement for the claims as they encompass a process for nucleic acid delivery to a cell *in vivo*, Applicant argues that the claims are fully enabled because, "the

location of the cell would not be expected to determine how the cell sees the DNA" (page 9). Applicant supports this assertion by citing teachings in Slattum *et al.* (*Id.*) and in the examples that demonstrate that the method can be used to obtain reporter gene expression *in vivo*. Applicant agrees with the Examiner's position that delivery of a therapeutic gene to a cell *in vivo* to achieve a therapeutic effect is not fully enabled, but asserts that the claimed invention is not gene therapy. Applicant states, "Applicants' invention is the delivery of a nucleic acid to a cell wherein the nucleic acid has been chemically modified within an expressible sequence, which is not the equivalent of delivering a nucleic acid to the cell for the purposes of gene therapy" (page 10).

These arguments have been fully considered but are not found persuasive. The Examiner's position is not that the specification does not teach how to introduce a nucleic acid into a cell *in vivo*, but that the specification does not provide an enabled use for that method. The enabling disclosure must teach the skilled artisan how to use the full scope of the claimed invention. To the extent that the claimed method is practiced *in vivo*, the specification provides a single specific, substantial and credible utility: gene therapy. In the paragraph bridging pages 2-3, Applicant teaches gene therapy by expression of a whole or partial protein or antisense. On page 3, Applicant contemplates gene replacement therapy of Duchenne muscular dystrophy, as well as treatment of neurodegenerative disorders, cancer, heart disease and infections using the claimed invention. Applicant further teaches expression of therapeutic genes such as erythropoietin, FGF and VEGF. Although the claims are not limited to gene therapy, it is clear from the disclosure that the intended use for the claimed method is gene therapy, and that the method is to be used for gene therapy of extremely complicated diseases such as muscular

dystrophy, neurodegenerative disorders, cancer and heart disease. As the disclosure clearly indicates that the claimed invention is to be used for gene therapy, the enabling disclosure must teach the skilled artisan how to use the method for that purpose. However, for the reasons set forth in the previous Office Action, the disclosure fails to teach the skilled artisan how to use the claimed invention for the purpose clearly stated therein.

Applicant's argument, "[t]he nature of the expressible nucleic acid and purpose for which it is delivered does not affect the claimed process..." misses the point of the rejection which is that the nature of the expressible nucleic acid and purpose for which it is delivered is central to the question of how the method is used, which must be fully enabled by the disclosure. Delivering a nucleic acid to a cell is not in and of itself a patentable utility. Instead, the disclosure must teach how delivering a nucleic acid to a cell is to be applied to a real world problem. In the instant case, the specification teaches only that the claimed method practiced *in vivo* is to be used for gene therapy, which, for reasons of record, is not enabled by the disclosure. Therefore the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

New Grounds Necessitated by Amendment

Claim Objections

Claim 1 is objected to because of the following informalities: In part (c), there are two articles (i.e., "a" and "the") preceding "modifying". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite the recitation of "nucleic acid modifying agent" in part (b). As the claims have been amended such that a "nucleic acid modifying agent" instead of a "compound" is attached to the nucleic acid, it would seem that the nucleic acid modifying agent is somehow different from the compound of the original claims. The specification provides no definition of a nucleic acid modifying agent, and the naming of such compounds such as enhanced immune response molecules, which would not usually be considered nucleic acid modifying agents, in the dependent claims suggests that Applicant's definition of a nucleic acid modifying agent is somehow different from what is generally understood in the art.

Claims 3, 5 and 6, and claim 4 as it depends from claim 3, are additionally indefinite in the recitation of "the compound", there is insufficient antecedent basis for the limitation in the claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
August 12, 2003

JAMES KETTER
PRIMARY EXAMINER